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09/470,278 12/22/99 KOLODNER

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EXAMINER

FREDMAN, J

ART UNIT	PAPER NUMBER
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1655
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/470,276	Applicant(s) Kolodner et al
Examiner Jeffrey Freedman	Art Unit 1655



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on May 10, 2001

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-40 is/are pending in the application.

4a) Of the above, claim(s) 1 and 13-38 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 2-12 and 39 is/are rejected.

7) Claim(s) 40 is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) Notice of References Cited (PTO-892)
16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) Information Disclosure Statement(s) (PTO-1448) Paper No(s). _____

18) Interview Summary (PTO-413) Paper No(s) _____

19) Notice of Informal Patent Application (PTO-152)

20) Other: _____

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DETAILED ACTION

General

1. Claims 2-12 utilize the transitional term "having". Because this term lacks any particular meaning in the patent literature, the examiner will interpret "having" as being equivalent in scope to the open term "comprising".

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 5-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims are drawn to one of two broad genus, claims 5-9 being drawn to a genus comprising any DNA segment which hybridizes to a fragment of 17 contiguous nucleotides of SEQ ID NO: 1 and claim 10-11 being drawn to any primers which permit synthesis of a human mismatch repair gene, particularly hMSH5. This large genus is represented in the specification by only the named SEQ ID Nos. Thus, applicant has express possession of only one full length nucleic acid species and shows no fragments which are demonstrably unique and shows multiple primers in a genus which comprises hundreds of millions of different possibilities. The written

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description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided.

Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only specific nucleic acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted that in *Fiers v. Sugano* (25 USPQ2d, 1601), the Fed. Cir. concluded that

"...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the nucleic acid and inherent amino acid sequence of the disclosed SEQ ID Nos are described. Also, in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111, CAFC 1991), it was concluded that:

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"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any nucleic acids acids which comprise "unique fragments" or which are modified by addition, insertion, deletion, substitution or inversion with the disclosed SEQ ID Nos.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2-6, 8, 9 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Sargent et al (EMBO J. (1989) 8(8):2305-2312).

Sargent teaches cosmid vectors which are transformed into E. Coli host cells (page 2311, column 2) which cosmid vectors comprise a double stranded nucleic acid (necessarily including sense and antisense strands) that includes the "G7" gene (page 2306, figure 1). Within figure 1, several cosmid vectors overlap the "G7" gene including F9N, F12M, FMC, FME and EL3. The "G7" gene is inherently found to be the MSH5 gene claimed. With regard to points of similarity, the "G7" gene is located on chromosome 6p21.3 as is the MSH5 gene, and the following is a

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partial sequence comparison of MSH5 and "G7", where MSH5 is the Qy sequence and "G7" is the database sequence.

Query Match 89.5%; Score 2596; DB 68; Length 3998;
 Best Local Similarity 97.1%; Pred. No. 0;
 Matches 2675; Conservative 0; Mismatches 30; Indels 51; Gaps 1;

Qy	184	tgcggccacaggccctcagacecccttcattccaaaggagccctccaaagctcatggccctcc	243
Db	6	TCGGTCAGCGGGGGGGTTCTCCACCTGTAGCGACTCAGAGCCTCCAGCTCATGGCCCTC	65
Qy	244	ttagggcgaacccaaagggacacccgcggccacccggacacttggggccctccctccgg	303
Db	66	TTAGGAGCGAACCCAGGAGACCCGAGGGACCTGGGAGACCTGGGGGGCCCTCCCTCCGGC	125
Qy	304	tcccccagcccgcccccaagtgcggcccccacggggaggccggggaggaaatgcggagg	363
Db	126	TCCCCAGCCCGGCCCACTGGCCGGGCCCAAGGGAGGCCAGGGAGGGAGTCGAGGAG	185
Qy	364	gaggaggaggctggccagatccatctgttgtgtgtggaaatttccggatacttggccatt	423
Db	186	GAGGAGGAGCTGGCCAGATCCATCTGTGTGTCTGTGGAATTCAAGGATACTTGGCCATT	245
Qy	424	gcctactatgtatactgtactgccttccactatccacttcatgccecatgcggccacacag	483
Db	246	GCTTACTATGTATCTGACTGACTCCACTATCCACTATGCCAGATGCCAGATGCCAGACCA	305
Qy	484	agccctaaagtttccagagatgttctggatgagatcaatccccatctgttgttacggat	543
Db	306	AGCCTAAAGCTTCTCAAGAGATCTGGATGAGATCAATCCCAGTCGTGTTACGGAT	365
Qy	544	cccaaaacaggatggaaataatgtactcgatcttcgtggaaaggctggccctccaggac	603
Db	366	GGCARACAGGATGAGATGACTCTGGATTCTGGAAAGCTTCTGCCAGGGACACAGA	425
Qy	604	ggccctaaagccatgtatcttccatccatccatccatccatccatccatccatccatccat	663
Db	426	GAGCTAAAGNCCTGAATCATATTTCGCAAGTGTGGATTGGCTGGAGATAAGC	485
Qy	664	aaaaacacgccttccttcgtggaaataactccatccatccatccatccatccatccat	723
Db	486	AAACAACGCCCTCTTCGGAAACTCTCCATCCCAGACGCCATGACTGCCACTGAG	545
Qy	724	aaaaatcccttccttccttcgtggatccatccatccatccatccatccatccatccat	771
Db	546	AAATCCTCTCCCTCTCCATATTCCCTTGACTGCCCTCACACCCCCAGGGAGAT	605
Qy	772	-----gtcgacgcacttggggctg	792
Db	606	TAAAGATTACCCCGATTCCACTGCTGATCCCCCTCCAGGTTCGACCCACTGGAGGCC	665
Qy	793	ctgaaggatccgggtcgaagaaatccgggttgcactggaaatctatgtcgacgtc	852
Db	666	CTGAAGTTCCTGGTGTGAGAAGAATCGGGTTGAACTGGAAAGCTATAATGTCAGC	725
Qy	853	cccatccctgggttaagaaattttgtgtactcatctggtaacatagatcaagacact	912
Db	726	CCCATCTGGCTTAAGAAATTATGTGACTCATCTGTGAAACATAGATCAAGACACT	785
Qy	913	tacagtgttctacagattttaagatgtgtactcatctggtaacaaatgtggccagt	972

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DB 2706 GTTTCTCTAGAAATTTGTTTCATATTAGGAATAAAGTTATTTGAAGAAAGATA 2761

Therefore, it clearly appears that the Sargent cosmid vectors anticipate the current claims as inherently comprising the MSH5 gene sequence.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albertella (Genomics (1996) 36:240-251) in view of Stratagene Catalog (1988) p. 39.

Albertella teaches a number of primers which function to amplify the "G7" gene region (page 241, column 2, subheading "reverse-transcription-PCR" to page 242, column 1). As discussed above, "G7" is inherently found to be the MSH5 gene.

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Albertella does not teach placement of these reagents into a kit format, nor the specific SEQ ID Nos: 3-50.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the primers of Albertella into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantitites of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to identify functionally equivalent primers and probes selected from the sequences disclosed by Albertella for detection of the "G7" gene.

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In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the court stated

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are suggested by the prior art as useful for primers and probes, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

8. Claims 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sargent et al (EMBO J. (1989) 8(8):2305-2312) in view of Beach et al (U.S. Patent 6,025,192).

Sargent teaches cosmid vectors which are transformed into E. Coli host cells (page 2311, column 2) which cosmid vectors comprise a double stranded nucleic acid (necessarily including sense and antisense strands) that includes the "G7" gene (page 2306, figure 1). Within figure 1, several cosmid vectors overlap the "G7" gene including F9N, F12M, FMC, FMEa nd EL3. The

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"G7" gene is inherently found to be the MSH5 gene claimed. With regard to points of similarity, the "G7" gene is located on chromosome 6p21.3 as is the MSH5 gene, and above is listed the partial sequence comparison of MSH5 and "G7", where MSH5 is the Qy sequence and "G7" is the database sequence.

Sargent does not teach placement of the G7 gene into a retroviral vector.

Beach teaches placement of genes into retroviral vectors for the elucidation of mammalian gene function (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to put the unknown G7 gene of Sargent into the retroviral vector of Beach since Beach states "The present invention relates to methods and compositions for the elucidation of mammalian gene function (abstract)". An ordinary practitioner would have been motivated to use the retroviral vector of Beach to identify the function of G7.

Response to Arguments

9. Applicant's arguments filed May 10, 2001 have been fully considered but they are not persuasive.

Applicant argues that the amendment to claims 5 and 9 has rendered the 112, first paragraph rejection moot. Applicant specifically argues that the specification gives extensive guidance on selection of human MSH5 primers for synthesis of a human MSH5 gene. This argument is not found persuasive because the claim expressly encompasses mutations not taught

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or suggested by the specification. For example, the Bawa reference cited in the Information Disclosure Statement teaches a human MSH5 gene different from that of applicant, due to the presence of a mutation in the MSH5 gene. While this reference is not prior art to the current application, it clearly teaches a human MSH5 gene which is not taught in applicant's specification, but which applicant seeks to capture by the broad claims. As the court noted in University of California v. Eli Lilly and Co, 43 USPQ2d 1398 (CAFC 1997),

"In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers , 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder , 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outline [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of

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knowledge as to what that material consists of, is not a description of that material.

[6] Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

In the current case, the claims attempt to distinguish the differences solely by function, with no structural features identified in the specification and no structural features identified in Applicant's response.

With respect to the art rejections, Applicant's arguments are inapposite to the central question of anticipation. The issue is whether the cosmids, taught by Sargent in the EMBO paper, comprise an isolated nucleic acid sequence of SEQ ID NO: 1 or 17 basepairs of SEQ ID NO: 1 or the primers described. The publication date of the sequence is not relevant, since the cosmids themselves remain prior art, whether their sequence was known before or after the invention date.

Applicant appears to admit that the hMSH5 gene is within the cosmid on page 5 of the response, stating that "a 2.9 kb gene that lies within a 541 kb region." Applicant chooses to rely on the word "isolated" to argue that the claim does not encompass the plasmid. Applicant's

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claims (with the exception of claim 40, which is structurally different due to the cDNA language) are of the open "comprising" format. Applicant should note that MPEP 2111.03 states

"The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts")."

Clearly, the cosmid comprises the smaller sequences. The use of the word "isolated" or "purified" does not detract from that fact.

Applicant's remaining arguments are based on the same reasoning and have been already addressed above.

Allowable Subject Matter

10. Claim 40 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

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Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).



Jeffrey Fredman
Patent Examiner
Art Unit 1655

June 20, 2001